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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/348,469	SMITH ET AL.	
	Examin r	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sh t with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-24,26-34,41,42 and 47-74* is/are pending in the application.

4a) Of the above claim(s) *30,31,54,55 and 61-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,26-29,32-34,41,42,47-53,56-60,73 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0903* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission received on 9/5/03 has been entered.

Claims 22, 27, 32, 34, and 41-42 have been amended. New claims 47-74 have been added. Claims 22-24, 26-34, 41-42 and 47-74 are pending. Claims 22-24, 26-29, 32-34, 41-42 and 47-74 are under current consideration.

It is noted that claims 35-40 have been presented and listed as withdrawn in the amendment received on 9/5/03. However, claims 35-40 have been previously cancelled. See the amendment received on 9/29/00. Accordingly, the amendment received on 9/5/03 does not comply with 37 C.F.R. 1.121 but the apparently inadvertent error did not preclude examination of the instant application.

Election/Restrictions

Claims 30-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Newly submitted claims 54-55 and 61-72 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: as

set forth in the restriction requirement of 3/30/00, the methods of the claimed invention were separated from the transgenic animals of the claimed invention (the newly presented claims directed to cells can be interpreted to read on transgenic animals as such claims clearly read on cells *in vivo*).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 54-55 and 61-72 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Thus, claims 22-24, 26-29, 32-34, 41-42, 47-53, 56-60, and 73-74 are under current examination.

Priority

With respect to claims new added claims 47-53 and 56-60, Applicant's claim of priority to 08/537,765 now US patent 6,150,169 is denied. The parent application fails to fulfill the requirements of 35 U.S.C. 120 by not meeting the requirements of the first paragraph of 35 U.S.C. 112, particularly written description and new matter, necessary to support the claims of the instant application. In particular the following claim limitations are not described in the instant specification: a DNA construct comprising the sequence 5' A-P-B-Q-C 3'. See the rejections under 35 U.S.C. 112, 1st paragraph.

With respect to claims 22-24, 26-29, 32-34, and 41-42 as amended, Applicant's claim of priority to 08/537,765 now US patent 6,150,169 is granted.

Claim Rejections - 35 USC § 112, 1st paragraph

The following New Matter rejection has been necessitated by Applicant's amendments to the claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-53 and 56-60 as newly added are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 47 (and claims depending therefrom) is directed to a method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a DNA construct, wherein the DNA construct lack a promoter, and comprises the sequence: 5' A-P-B-Q-C 3' in which P is an internal ribosome entry site (IRES), Q is the heterologous gene sequence, and A, B, and C are, separately, optional linker sequences, wherein the DNA construct further comprises a polyadenylation signal at the 3' end of Q and a splice acceptor site located 5' of Q.

Claim 56 (and claims depending therefrom) is directed to a DNA construct comprising the sequence: 5' A-P-B-Q-C 3' in which P is an internal ribosome entry site

(IRES), Q is the heterologous gene sequence, and A, B, and C are, separately, optional linker sequences, wherein the DNA construct further comprises a polyadenylation signal at the 3' end of Q and a splice acceptor site located 5' of Q.

The specification provides no implicit or explicit support for a DNA construct comprising the sequence: 5' A-P-B-Q-C 3' in which P is an internal ribosome entry site (IRES), Q is the heterologous gene sequence, and A, B, and C are, separately, optional linker sequences, wherein the DNA construct further comprises a polyadenylation signal at the 3' end of Q and a splice acceptor site located 5' of Q. The specification, on page 6 and throughout, has only provided support for a DNA construct comprising the sequence 5' X-A-P-B-Q-C-Y 3' but not a DNA construct comprising the sequence 5' A-P-B-Q-C 3' is supported by the specification. Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should

conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure* [or point to case law supporting incorporation of such a limitation as in the instant case]".

The previous new matter rejection of claims 22-24, 26-29, 32-34, and 41-42 has been withdrawn.

Claims 47-53 and 56-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The previous enablement recited on pages 7-11 of the Office action mailed on 2/6/03 embraces issues relating to newly added claims 47-53 and 56-60. For clarity the aspects of the previous enablement rejection that apply to newly added claims 47-53 and 56-60 are reiterated below.

The claims are directed to a method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse cell with a random gene trap vector comprising a DNA

construct, wherein the DNA construct lacks a promoter, and comprises the sequence 5' A-P-B-Q-C 3', in which P is an internal ribosome entry site (IRES); Q is the heterologous gene sequence, including a translation start codon; and A, B and C are, separately, optional linker sequences. The claims are further directed to a mouse embryonic stem cell comprising a heterologous gene coding sequence inserted by the above method and a DNA construct, wherein the DNA construct comprises the sequence 5' A-P-B-Q-C 3' as above.

The specification has taught a DNA construct comprising the sequence 5' X-A-P-B-Q-C-Y 3', wherein X and Y comprise nucleotide sequences that are homologous to an endogenous gene in a mouse cell, P is an internal ribosome entry site (IRES); Q is the heterologous gene sequence, including a translation start codon; and A, B and C are, separately, optional linker sequences. The specification has also taught the creation of transgenic mice comprising the same construct, wherein the construct was introduced into ES cells to produce chimeric mice. However, the specification has not taught a DNA construct comprising the sequence 5' A-P-B-Q-C 3'. Moreover, the specification has not taught a method of inserting a heterologous gene coding sequence into an endogenous mouse cell genome using a DNA construct having the sequence 5' A-P-B-Q-C 3' or a mouse cell comprising a DNA construct having the sequence 5' A-P-B-Q-C 3'. The instant specification has not even provided a working example directed to a mouse cell transfected *in vitro* with the claimed DNA construct, 5' A-P-B-Q-C 3'. As such, in light of the teachings of the specification, which are directed to the creation of

transgenic mice, there do not appear to be any other disclosed uses for the claimed DNA construct or method than for the creation of transgenic mice.

As a first issue, the instant specification has not provided any guidance that would enable the skilled artisan to practice the claimed invention. In particular, the construct embraced by the claims is not disclosed in the instant specification. More particularly, the claim limitations of a DNA construct comprising 5' A-P-B-Q-C 3' are not disclosed in the specification. As such the claimed construct has not been taught. Moreover, the skilled artisan would not know how to use the claimed invention because it has not been disclosed in the instant specification. The guidance and working examples provided by the instant specification are directed to making and using a different DNA construct. While the instant specification teaches the creation of transgenic mice, use of the claimed construct in that context has not been disclosed. However, if one of skill were contemplating the creation of transgenic mice with the claimed construct the issues of unpredictability related to such are discussed in on pages 11-12 of the Office action mailed on 7/5/02. See Wall and Houdebine. Given, the lack of guidance provided by the instant specification it would have required undue experimentation to use the claimed invention.

Claims 52-53 are directed to mouse embryonic stem cells comprising the DNA construct encompassed by the claims, having the sequence 5' A-P-B-Q-C 3'. The claims as written do not recite isolated cells, and can be interpreted to read on a transgenic mouse when taken with the teachings of the specification. However, as the instant specification has not taught the creation of a single transgenic mouse comprising

the recited construct as mentioned above or a cultured cell comprising the recited construct the claims are not enabled.

Claims 47-53 and 59 are directed to a method for inserting a heterologous gene coding sequence into an endogenous gene in a mouse cell genome and mouse cells produced by the method. The method requires inserting a heterologous gene coding sequence into an endogenous gene and is interpreted to read on insertion of a heterologous coding sequence by homologous recombination. The claims however do not require that the recited construct comprise sequences that are homologous to the endogenous gene sequence. As such it is unpredictable if the heterologous coding sequence can be inserted into an endogenous gene because heterologous gene sequences (for example, transgenes) unless specifically designed for homologous recombination will randomly integrate into a host genome. Random integration does not necessarily include integration into endogenous genes. See Wall and Houdebine on pages 11-12 of the Office action mailed on 7/5/02. If by chance random integration resulted in incorporation of the claimed construct into an endogenous gene, the specification has not provided any guidance for determining which endogenous gene has incorporated the claimed construct. Moreover the claims as written would require nothing more than trial and error experimentation to successfully introduce the claimed DNA construct into an endogenous gene. Given the lack of recited homologous sequences in the claims it would have required undue experimentation for one of skill in the art to insert a heterologous coding sequence into an endogenous gene in a mouse cell genome as claimed without a reasonable expectation of success.

Given the lack of guidance, relevant teachings, and the absence of working examples, it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

The enablement rejection over claims 22-24, 26-29, 32-34, and 41-42 has been withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 47-50, 52-53, and 56-57 are rejected under 35 U.S.C. 102(e) as being anticipated by Tessier-Lavigne et al (US 6,248,934).

Tessier-Lavigne et al teach a DNA construct comprising the following elements from 5' to 3': a splice acceptor site, an IRES sequence, a heterologous nucleotide sequence, and a polyadenylation signal, wherein the construct is promoterless. See figure 1a, column 2 lines 25-31, and column 5 lines 29-33. Tessier-Lavigne et al also teach that the construct integrates into a gene in a cell, wherein the cells may be mouse embryonic stem cells. See columns 7-8 as well as the claims.

Accordingly, the teachings of Tessier-Lavigne et al meet all of the instant claim limitations.

The previous rejection of claims 22-24, 26-29, 32-34, and 41-42 under 35 U.S.C. 102(e) has been withdrawn.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-24, 26-29, 32-34, 41-42, and 73-74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 1-29 of U.S. Patent No. 6,150,169. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims embrace a DNA construct comprising the sequence 5' X-A-P-B-Q-C-Y 3', wherein X and Y comprise nucleotide sequences that are homologous to an endogenous gene in a mouse cell, P is an internal ribosome entry site (IRES); Q is the heterologous gene sequence, including a translation start codon; and A, B and C are, separately, optional linked sequences, methods of inserting a heterologous gene into an endogenous gene into a mouse embryonic stem cell genome, and mouse embryonic stem cells comprising the same construct. Therefore, the claims of US 6,150,169 would anticipate the claims of the instant application.

The Examiner acknowledges Applicants desire to file a terminal disclaimer to claims 22-24, 26-29, 32-34, 41-42, and 73-74, as they have priority to application 08/537,765, once a notice of allowance has been issued. See page 20 of the Amendment received on 9/5/03. In response, however, the Examiner submits that Applicants should file a terminal disclaimer prior to issue of a notice of allowance as the claims will not be allowed without submission of a proper terminal disclaimer. The requirement for submission of a proper terminal disclaimer cannot be held in abeyance.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER